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Carl R. Schwartz, Reg. No. 29,437

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Christopher M. Dobson
Serial No.: 09/787,560
Filed: June 4, 2001
For: FIBRILS
Examiner: Christopher J. Nichols
Art Unit: 1647

Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Attn: Mail Stop Amendment

Dear Sir:

DECLARATION

The undersigned declares that:

1. I, Professor Fred E. Cohen, am a U.S. citizen residing in San Francisco, California. I received a B.S. degree in Molecular Biochemistry and Biophysics from Yale University, a D.Phil. in Molecular Biophysics from Oxford University, and an M.D. from Stanford Medical School. I have also completed a postdoctoral fellowship, medical residency and endocrinology fellowship at the University of California, San Francisco (UCSF), and served as Chief of the Division of Endocrinology and Metabolism at UCSF for four years. I currently hold the position of Professor of Cellular and Molecular Pharmacology, Medicine, and Biochemistry and

Biophysics at the University of California, San Francisco.

2. I have researched and worked in the area of computational biology, using computers as a tool to investigate the relationship between protein sequence and structure, and to design drugs based on this information. More recently, I have researched and worked with Dr Stanley Prusiner on the molecular basis of prion replication. This has focused in particular on the prion diseases, the protein folding that is involved in these diseases, and the development of potential diagnostic and therapeutic methods for prion diseases.

3. I confirm that I have read the patent application published as WO 00/17328, which I understand was then presented as the national phase application listed above. I have also read the set of claims attached hereto as Exhibit A which I understand will be submitted herewith in relation to this application.

4. I believe that by virtue of these experiences I have an appropriate basis for opining, and it is my opinion, that:

(a) those of ordinary skill in the art as of September 21, 1998 would be broadly enabled by the application to practice the inventions claimed in the attached set of claims; and

(b) those of ordinary skill in the art as of September

21, 1998 would believe that Mr. Dobson was in possession of the inventions claimed in the attached set of claims, after reading the above application.

5. I have a particularly clear recollection of my perceptions about the state of the art of the field of protein folding as of September 21, 1998, insofar as amyloid fibrils are concerned. In this regard, around September of 1998 a number of research groups were working in the field of abnormal protein folding. A number of medical conditions had been identified which were believed to involve the formation of such fibrils *in vivo*.

6. There was evidence that many proteins could undergo a substantial change in shape (largely alpha helical to largely beta sheet), and that when this happened *in vivo*, a disease was often present. The actual causal relationship between fibrils and disease was unclear at that time. It was felt that most proteins would not form fibrils because the list of diseases in which fibrils had been identified was relatively small, and the number of proteins that were associated with these deposition diseases was of a similar magnitude.

7. Several groups were then working with proteins associated with deposition diseases and were trying to artificially form fibrils. Particularly notable were work by

Lansbury and co-workers on A-beta in Alzheimer's disease and the work of my own laboratory (Cohen, Prusiner and co-workers) on prion disease. These studies were intended to investigate the mechanism by which fibrils were formed from those native proteins *in vivo*. These studies used proteins which were known to form fibrils *in vivo*, or fragments or variant forms of those proteins. Even though the peptides used were all derived from proteins that were already known to be fibril competent, in general the experiments carried out in our laboratories indicated that even with respect to them some of the peptides formed fibrils and others did not.

8. There were a variety of morphologies associated with the fibrils that were formed. Some corresponded to the native protein "biological" fibrils, while others did not. Some fragments of the native fibril competent proteins were believed to be unable to form fibrils themselves. This work clearly suggested to those of ordinary skill that the ability to form fibrils was restricted to a particular subset of proteins.

9. I became aware of the work of the inventor Chris Dobson, and his laboratory, at about that time. This work was considered surprising not only by me, but also by others working in this field. This work provided for the first time a general basis for believing that fibril formation was an

intrinsic part of the structural chemistry of the polypeptide backbone and could therefore be made applicable, in principle, to any protein.

10. I believe that the implication of the Dobson work is that amino acid sequences had evolved to protect against fibril formation. However, by exposing them to the right conditions it is possible to destabilize the "evolved" native state and reach a state that in appropriate conditions of, for example, temperature, alcohol, or acetonitrile, and given the right amount of time, fibrils would form.

11. This discovery, that all proteins are ultimately capable of forming fibrils if exposed to the right conditions, was unexpected and had not been predicted based on the work carried out in my own or other laboratories that I am familiar with. Evidence as reported in the present application, and as later reported in other literature reports, supports this concept of the breadth of enablement. This was first demonstrated by Professor Dobson in work, as reported in the present patent application, using an SH3 domain, and was later confirmed in his experiments with myoglobin, a very soluble alpha helical protein that no one would have previously expected to be "fibril competent".

12. The key point here was the Dobson realization that it would, in fact, be possible to form fibrils from, in

principle, any protein. As explained above, prior to this, it was assumed that the ability to form fibrils was restricted to only a subset of proteins and there would therefore have been little motivation to carry out the experiments needed to produce fibrils from a randomly selected protein.

13. In any case, because the formation of fibrils was not, in general, expected to occur, there would be no motivation to persevere with even routine experiments if initial studies were unsuccessful. It would simply have been assumed that the selected protein was not "fibril competent".

14. Once the knowledge existed due to the present inventor that fibril formation was possible, and the examples of the present application were available, I believe that a relatively standard approach could be taken to identify enabling (and even particularly desirable) fibril forming conditions for a selected peptide or protein. The actual experiments that would need to be carried out would be straightforward: simply a matter of varying the conditions in which the protein is incubated.

15. As suggested in the patent application, factors such as temperature, protein concentration, pH and the presence of alcohols or denaturants could easily be tested for effect with the starting point being the exemplified conditions. As a researcher in this field at the time, I would have been aware

as of September 21, 1998 (with the benefit of the present application) of varied factors that could be tested for an effect on the protein conformation. However, a variety of different conditions or combinations could be tested systematically in order to optimize a suitable set of conditions for fibril formation in a selected protein.

16. High throughput formats were standard technology and could have been used to speed this process for any particularly problematic protein if any were found. Moreover, there are a variety of alternative methods which have been developed to quickly screen for fibril formation, such as Thioflavin T binding, which can make even simpler the process of analysis. I do not believe that this process would be unduly burdensome or require unreasonable levels of experimentation.

17. After reviewing the specification, and in light of my understanding of what the art knew as of September 21, 1998, and also in view of my awareness generally of the research of the Dobson lab relevant to the attached claims at about that time, I believe it clear that Chris Dobson did have possession of the attached claim subject matter. Moreover, I believe that just from the application itself one skilled in the art would believe that Chris Dobson had possession of the attached claim subject matter.

The undersigned declares further that all statements made herein based on personal knowledge of the undersigned are true, that all statements made herein based on information from third parties are believed to be true, and further that all these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 U.S.C., and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: October 1, 2004

Fred E. Cohen

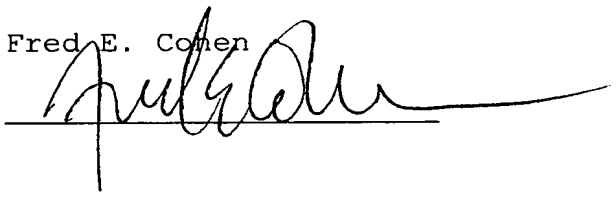

Exhibit A

38. A process for preparing an amyloid fibril, which process comprises:

a first step of preparing a solution comprising a protein, said solution being in a state so that nucleation and growth of a non-naturally occurring fibril can occur, and

a second step of allowing nucleation and growth of the non-naturally occurring fibril to take place.

39. A process according to claim 38 wherein the solution further comprises an alcohol.

40. A process according to claim 38 wherein the solution further comprises alcohol selected from methanol, ethanol, propanol, butanol, trifluoroethanol and hexafluoroisopropanol.

41. A process according to claim 38 wherein the solution further comprises acetonitrile.

42. A process according to claim 38 wherein the solution further comprises urea.

43. A process according to claim 38 wherein the concentration of protein in the solution is from 0.1 mM to 10 mM.

44. A process according to claim 38 wherein the temperature of the solution is from 0°C to 100°C.

45. A process according to claim 38 wherein the solution

is acidic.

46. A process according to claim 38 wherein the pH of the solution is from 0.5 to 6.5.

47. A process according to claim 38 wherein the solution is seeded with previously formed particles of protein.

49. A process according to claim 38 wherein the non-naturally occurring amyloid fibril prepared by said process comprises a metal.

50. A process according to claim 49 wherein the metal is selected from the group consisting of copper, silver and gold.

54. A process according to claim 38, wherein said solution is treated to denature or partially denature the protein.

55. A process according to claim 54, wherein said denaturing is effected by treatment with an alcohol, aliphatic nitrile or urea, reducing the pH, or by shaking, agitation or exposure to a glass or plastic surface.

56. A process according to claim 38, wherein the solution further comprises an alcohol at 5 to 40% v/v.

57. A process according to claim 38, wherein the solution further comprises an aliphatic nitrile at 5 to 95% v/v.

58. A process according to claim 38, wherein the solution further comprises urea at 4 to 7 M.

59. A process according to claim 38, wherein nucleation

is achieved by varying the pH and/or ionic strength of the solution.

60. A process for preparing an amyloid fibril, which process comprises:

preparing a solution comprising a protein, said solution being in a state so that nucleation and fibril growth will occur, wherein the pH of the solution is from 0.5 to 6.5, the temperature of the solution is from 0°C to 100°C, and wherein the solution optionally also comprises an additive selected from the group consisting of an alcohol at 5 to 40% v/v, an aliphatic nitrile at 5 to 95% v/v and urea at 4 to 7 M; and

allowing nucleation and fibril growth to take place;

wherein a non-naturally occurring amyloid fibril is prepared by said process.

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